INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

March 2020

Comic Corner

Stigma And Infodemic:
Why Do We Create Our Enemies?

TRIPOD and INA-PROACTIVE
Studies' Updates

FROM OUR LABORATORY

Respiratory Syncytial Virus:
In-Depth Review (Part 2)

Data Management
Helpful Site Tips
to Minimize Data Queries
(from Your "Data Manager")

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2020

INA-RESPOND newsletter

MASTHEAD

EDITOR-IN-CHIEF

M. Karyana

EXECUTIVE EDITOR

Herman Kosasih

CREATIVE DIRECTOR

Dedy Hidayat

ART DIRECTOR

Antonius Pradana

SENIOR WRITERS

Aly Diana

REVIEWERS & CONTRIBUTING WRITERS

Dedy Hidayat, Eka Windari R., Herman Kosasih, Kanti Laras, Lois E. Bang, Maria Intan J., M. Ikhsan Jufri, Mila Erastuti, Neneng Aini, Nurhayati, Venty M. Sari

THANK YOU

INA-RESPOND Network & Partners

INA-RESPOND Secretariat

Badan Penelitian dan Pengembangan Kesehatan RI, Gedung 4, Lantai 5.
Jl. Percetakan Negara no.29,
Jakarta 10560

content

March 2020 Edition | issue #78

FEATURES

INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

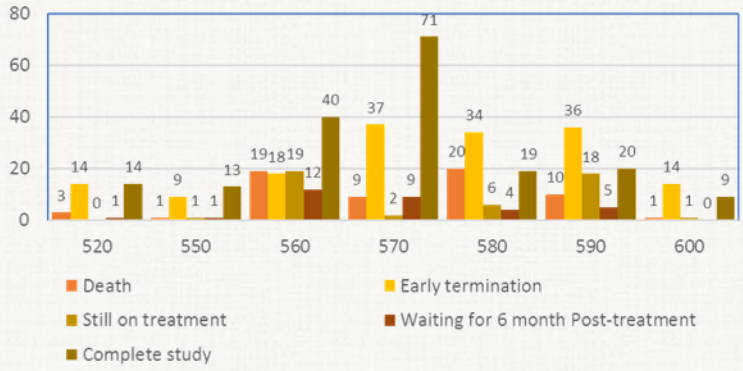


Figure 1.Participant status per site based on uploaded CRF per 4 Mar 2020

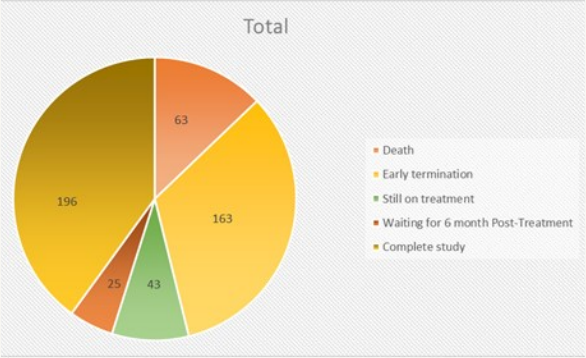


Figure 2. Total Participants Status based on uploaded CRF per 4 Mar 2020

INA102

PARTICIPANT STATUS

Per 04 March 2020, the total ongoing participants in TRIPOD study are 68 out of 490 enrolled participants. From those 68 on-going participants, 43 are still on TB treatment while 25 are waiting for a 6-month post-treatment visit. One hundred sixty-six participants have completed the study, while 226 participants are terminated early (including death). Therefore, there are still 13.8 % of participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are: 1 participant from site 520 (RS Sanglah Denpasar) who still need to be followed up, 2 participants from site 550 (RSUP dr. Wahidin Sudirohusodo Makassar), 25 participants from site 560 (RSUP dr. Kariadi Semarang), 8 participants from site 570 (RSUD dr. Soetomo Surabaya), 9 participants from site 580 (RSUP dr. Sardjito Jogjakarta), 22 participants from site 590 (RSUP Persahabatan Jakarta), and 1 participant from site 600 (RSUP dr. Adam Malik Medan).

INTERIM ANALYSIS AND RE-TESTING SAMPLE

There will be an interim analysis meeting in April 2020. Besides the study updates, the focus of the interim meeting analysis for the TRIPOD study is to discuss future plans and study publications. Study concepts from sites and manuscript writing guidelines will be the main concern for this meeting. Re-testing sample are now in progress. MTA submission has been prepared, and once approval is obtained, samples will be sent out to National Jewish Lab in Denver, Colorado.

Site number	Site name	Author
520	RS Sanglah Denpasar	dr. I Gede Ketut Sajinadiyasa, Sp.PD
550	RSUP dr. Wahidin Sudirohusodo	Dr. dr. Irawaty Djaharuddin, SpP(K)
560	RSUP dr. Kariadi	dr. Banteng Hanang Wibisono, Sp.PD-KP
570	RSUD dr. Soetomo	dr. Tutik Kusmiati, SpP (K)
580	RSUP dr. Sardjito	dr Bambang Sigit Riyanto, SpPD-KP, FINASIM
590	RSUP Persahabatan	dr. Diah Handayani, SpP
600	RSUP H Adam Malik	Dr. dr. Bintang YM Sinaga, M.Ked(Paru), Sp.P(K)

Table 1. Author List of TRIPOD Manuscript

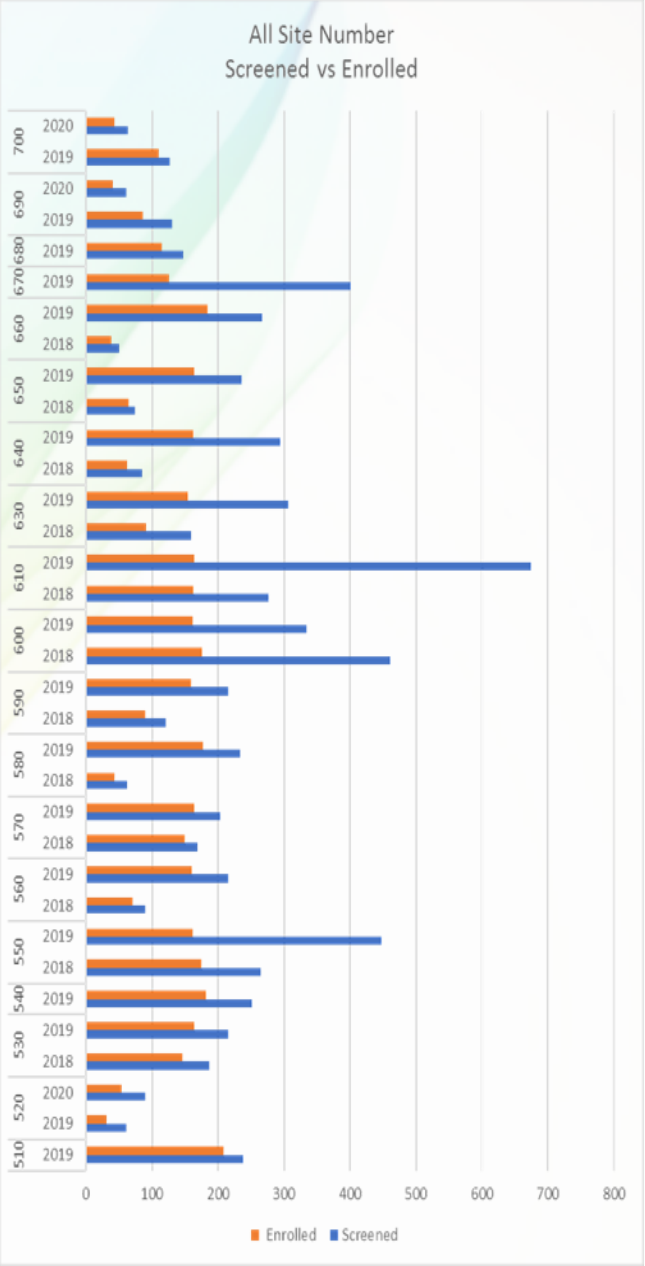
INA104

As of 15 March, from 19 Sites of PROACTIVE Study, 4,277 subjects were enrolled, which consist of 4.092 adult and 185 pediatric. The three last activated sites will continue to recruit new subjects until 30 June 2020. They are Site 700 (T.C. Hillers Hospital in Maumere), Site 690 (Abepura Hospital in Papua), and Site 520 (Sanglah Hospital in Bali).

From 4,277 subjects enrolled, 111 subjects are end of study due to some reasons, such as death cases, moved away, withdrawn consent, and HIV negative test result. Details end of study distribution per site is shown in Figure 2.

Following the suggestions during the Statistical Analysis Plan (SAP) meeting, the Secretariat needs to discuss strategical site management with the sites to resolve the data issues. Site Meeting is planned to be conducted in Jakarta on 11-12 Mar 2020. However, due to the Pandemic of Covid-19, this meeting is postponed and replaced with a video conference call meeting on 11 March 2020. All sites attended the meeting, represented by their Principal Investigator, Co-PI, and Research Assistants. At the same time, from Secretariat, INA-RESPOND Chairman and all members of PROACTIVE study (CRA, SS, and DM) were present. During the meeting, the study data manager explained the Data Management process, data submission status, data completeness and accuracy, missing log pages status, query status, and problems related to data management. At the end of the meeting, Secretariat gave the performance rate for each site based on data completion management and suggestion on how to overcome the site's problem.

Also, due to the Covid-19 pandemic, a notification by INA-RESPOND Chairman to the NSC members, PI, Co-PI, and study teams was released for all sites to temporarily halt screening, enrollment and follow-up activities of the PROACTIVE study effective 16-28 March 2020. Notification is also submitted to NIHRD Ethics Committee on 19 March 2020. This temporary suspension was made with the intention that the PROACTIVE study sites which have been appointed by the Minister of Health of the Republic Indonesia as Reference Hospital for the Prevention of Emerging Infection Disease may focus on providing services for COVID-19 patients.



Site Number	Subject		Total End of Study	Total Existing Subject
	Total Screened	Total Enrolled		
510	238	208	0	208
520	114	58	0	58
530	403	310	9	301
540	251	182	0	182
550	712	337	14	323
560	306	230	8	222
570	372	313	5	308
580	295	220	0	220
590	336	249	19	230
600	795	338	13	325
610	950	327	13	314
630	466	245	2	243
640	380	225	0	225
650	310	229	5	224
660	317	222	1	221
670	401	126	3	123
680	147	115	0	115
690	166	105	2	103
700	157	133	2	131
Grand Total	7116	4172	96	4076

Figure 2. Total end of study and existing subject

INA-RESPOND Newsletter

Helpful Site Tips to Minimize Data Queries (from Your "Data Manager")

By: Shera Weyers and Michael Duvenhage

Data queries are an incredibly important part of any study. However, the process of sending data queries to a site can quickly become a nightmare, not only for the site that might feel overwhelmed by the amount or type of data queries they are receiving but also for the data management team who have to keep on top of generating and tracking all the data queries until they get resolved by the site. Additionally, as the study moves closer to the database lock date, there will be a rush to complete the various data reviews which might results in large batches of queries being generated, not leaving a lot of time for the site to answer and return the queries to the data management team.

It is important to understand that the data query process is a crucial step in obtaining a high-quality database. Therefore, this process needs to be streamlined a much as possible. A question that is often asked is, 'Why does the Data Management team query the sites so often?' when they, i.e., the Data Management team, can see what the obvious answer should be. This might be true. However, considering the regulated environment of a clinical trial, a data manager may never assume data on behalf of the site and may never update the CRF (Case Report Form) without the direct permission of a site investigator or designee.

Most often, the majority of data queries are due to missing or discrepant data, which can be avoided if certain steps are performed throughout a study. This sounds easy. However, in a difficult clinical setting, where many patients are being cared for, possibly where many different studies are happening at the same site, the priority may not always be with CRF completion. All this may result in CRF completion delays as well as situations where the CRF might be completed incorrectly, or some data items are missed or overlooked.

However, please do not worry, since most of these frustrations can be avoided if the startup and conduct of the study are well planned. It is important to consider the following items as part of our data collection strategy for our study.

Review the CRF before the start of the study

The CRF is a vital step in the collection of clinical data for a study. The CRF must be harmonized with the protocol. In other words, the CRF should only record data that is required per the protocol and that the flow of the CRF corresponds with the study schedule as contained within the protocol. Do not collect data that is not required per the protocol. I will repeat – Do not collect data that is not required per the protocol! Often the collection of more data results in poor data collection since the study team might become too "stretched" to ensure that appropriate quality checks are implemented. It is essential to structure our data collection strategies around the

primary and secondary objectives of the protocol. Try to keep our data collection process as simple as possible. Remember that an excellent data collection tool will result in data being completed easily as well as efficiently.

Complete the CRF timely and accurately

Completion of the CRFs promptly will assist the study team in identifying missing or incorrect data in a timely manner. It is crucial to ensure that all source documentation is fully completed and available before the subject leaving the study site. The best practice is to complete the CRF on the same day as the subject visit whenever possible. This will result in CRF completion to not falling behind, and data may be submitted to the data management team on time.

We (your Data Managers) cannot overstate how important it is for us to get the data as early as possible. This will help us to identify any mistakes early on, which will allow us to provide the sites with any advice and guidance on some of the common mistakes that we are seeing. Additionally, this will also allow us to investigate any unexpected data problems that might be difficult to solve (some of these issues might have to be discussed with the PI and statisticians and thus may take many weeks to resolve).

Please make sure that when you complete the CRF that you follow the instructions in the CRF completion guidelines. If you do not have a CRF completion guideline for your study, then please ask your Data Managers for this document. All studies should have a CRF completion guideline, and you must be familiar with the contents of this document.

Ensure the individual completing the CRFs handwriting is legible. Do not use cursive writing. Any items or text that cannot be understood or read will have to be queried. This is something that can be avoided and will lead to a reduction in queries. Additionally, try to limit your free text and ensure data is completed inside the designated fields allocated for that information.

When completing dates, ensure they are in the correct format and are in the correct sequence per the CRF.

Lastly, and probably most importantly, please make sure that all CRFs are quality checked or reviewed prior to the CRFs being sent to the Data Management team. Ensure that any completion issues that the reviewer(s) identifies are correctly communicated to the team who is responsible for the completion of the CRFs. Make sure that each cycle of CRF completion is treated like a lessons-learned exercise. Do not focus on the mistakes, but rather on the lessons learned.

Understanding the query process

It is important to understand the query resolution process for the study. This process will usually be presented by the Data Management team during the study startup training or meetings. Ensure that you are fully aware of how queries will be sent to your site and what the expectation is on how those queries are to be answered and returned to the Data Management team.

When receiving queries from the Data Management team, it is important to understand the query message completely. If you do not understand the query text/ message, instead, contact your Data Manager before making any changes to the CRF. Incorrect CRF updates will result in more queries and will lead to further frustration and wasted time.

Make sure that any data updates you make to the CRF are done on the appropriate participant and in the correct visit. Any source documents must also be reviewed during the required update to the CRF.

Remember that it is a Good Clinical Practice (GCP) that any CRF changes that you make must be initialed and dated. Also, if you make any CRF changes (for whatever reason), the updated CRFs must be sent to Data Management to update the data in the database.

Responding to queries

Various queries can be sent to the site for clarification during the duration of the study. Most queries are due to missing data, which can easily be prevented should the CRF be completed as per instructions. However, other queries may require clarification on why something happened (e.g., why a participant visit is out of the window) or question a data item that seems incorrect/odd (e.g., a high lab value that could possibly be correct, but still looks strange enough to query).

When responding to these types of queries, be sure to provide the answer to the actual question that is being asked in the query. If you confirm the data is correct, please indicate why it is correct. If the data is not correct, please indicate that the data is not correct, and please also provide the correct data value.

Please take note that an update on one CRF page may result in an update on another CRF page. I.e., if you add a new Adverse Event due to a query, make sure that any associated Concomitant medication given for the treatment of that Adverse Event is also documented on the Concomitant medication or Treatment pages.

A final word from your Data Manager

Remember we are in this study together, we all have the same goal, which is high-quality data. We dislike queries as much as you do. Still, it is a necessary task to ensure that we end with a high-quality database that may assist the study team in answering the important protocol questions. We are here to help, so please contact us as soon as you have questions or think we can help in any way.

A Little About the Writers, Shera Weyers and Michael Duvenhage

Shera and Michael are employed by Leidos Biomedical Research, Inc. within the Division of Clinical Research at the National Institute of Allergy and Infectious Diseases. In their various roles they are supporting data management operations for emerging infectious diseases and other infectious diseases within Africa, Asia and the USA.

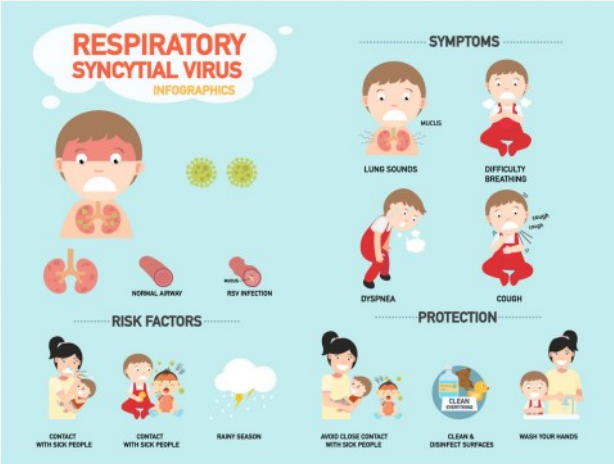
Photo: Michael Duvenhage (top) and Shera Weyers (bottom)

INA-RESPOND Newsletter

FROM OUR LABORATOIRY

RESPIRATORY SYNCYTIAL VIRUS: IN-DEPTH REVIEW (PART 2)

By: Yan Mardian



Who is at risk?

RSV infection is a leading cause of lower respiratory tract infections worldwide. The risk of severe RSV disease is increased by factors that compromise the ability to control and withstand a respiratory tract infection: young age (<6 months), premature birth (<35 weeks of gestation), multiple birth, male sex, malnutrition/small for gestational age, family history of atopy or asthma, bronchopulmonary dysplasia, congenital heart disease, immunodeficiency or immunosuppression, the first or second RSV infection in life, unusually narrow airways, low birth weight, male gender, a low titer of RSV-specific serum antibodies, low socioeconomic status and parental education, crowded living conditions, young siblings, maternal smoking and indoor smoke pollution, and frail old age.[1]

Prematurity goes along with small, immature, and vulnerable airways, an immature immune system, an incomplete transfer of maternal antibodies, and an inadequate cellular immunity, which is necessary for the viral clearance. Another study revealed that RSV- specific antibody titers were lower in premature infants of 28 weeks GA compared with term infants; and preterm infants of 29 weeks GA had RSV- specific titers against F and G protein comparable to those of term infants. High titers of maternally derived RSV neutralizing antibodies are inversely associated with the incidence of acute RSV LRI during the first six months of life.[2]

Infants show prolonged viral shedding and increased morbidity and mortality rates associated with RSV infection. Infants with Congenital Heart Disease are known to be at increased risk of severe illness from RSV infection regarding higher morbidity (more complicated clinical course, e.g., need for assisted ventilation or longer duration of oxygen supplementation) and higher mortality rate. Another group of infants being at increased risk for severe RSV infection is that with neuromuscular impairment. Factors predisposing to a more severe course of RSV disease in neuromuscular disease include the impaired ability to clear secretions from the airways due to ineffective cough resulting from respiratory muscle weakness and the high prevalence of gastro-oesophageal reflux and swallowing dysfunction, which leads to aspiration.[2]

Male sex is known to be a risk factor for severe RSV LRTI. An analysis of representative studies over the last 30 years found the risk ratio of boys to girls being 1,425:1. The reason, therefore, seems to be anatomic that boys have shorter and narrower airways and are more likely to develop a bronchial obstruction in case of RSV infection. Other demographic features, such as crowded living conditions and siblings, appear to be significant risk factors for more severe RSV LRTI and RSV related hospitalization. Reasons, therefore, include the increased likelihood of exposure to the virus and, subsequently, the increased risk for infection. Many studies demonstrated a significant effect of increased numbers of persons sharing a bedroom on RSV LRTI. This effect was increased in families with low maternal education and even more in families with low maternal education who had not breast -fed their babies. Also, patients with severe combined immune deficiency syndrome and those with acquired immune deficiency syndrome appear to be highly susceptible to severe, persistent infections due to a variety of microorganisms, of which viruses likely are the most common. RSV readily infects severely immunocompromised individuals, most notably allogeneic bone marrow transplant recipients, causing high mortality. [2]

RSV has now also conclusively been shown to be a significant cause of morbidity and mortality in the elderly and is being recognized as a threat worldwide. Although yearly attack rates are relatively low, the disease burden is large and growing with the aging population. Initially described as the cause of nursing home outbreaks of respiratory disease, there is a now significant body of literature describing the clinical importance of RSV in older adults in a multitude of settings, including long-term care, adult day-cares, and in community-dwelling adults. Furthermore, as medical care for malignant diseases is provided to increasingly older patients, elderly persons receiving cytotoxic therapy for acute leukemia or those who have undergone hematopoietic stem cell transplant (HSCT) or solid-organ transplant are at significant risk for severe RSV infections and fatal outcomes. Pneumonia and exacerbations of chronic medical conditions such as asthma, chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) are commonly associated diagnoses of RSV in older hospitalized patients.[3]

Diagnostic Test

Rapid laboratory diagnosis of RSV infection significantly decreases the use of antibiotics, additional laboratory testing, and is associated with shorter hospitalization periods. The specific diagnosis of RSV infection is based on the detection of virus or viral antigens or virus-specific nucleic acid sequences in respiratory secretions. The kind and quality of the clinical specimen exert a considerable influence on the results of all currently used viral detection assays. Antigen based tests are widely available, easy to perform, and the results are available in a short time, but their reduced sensitivity and specificity represent a considerable shortcoming. Among the methods available, isolation in cell culture was considered the gold standard for the sensitive identification of RSV, but it is gradually replaced by highly sensitive and specific nucleic acid amplification assays that provide more rapid results. Of these reverse-transcription polymerase chain reaction (PCR) was the first and is still the most frequently used nucleic acid-based assay.[4]

A significant challenge to making a diagnosis of RSV infection is that adults with reinfection shed virus at considerably lower titers and for a shorter duration of time than in children. Typically, adults shed virus in their nasal secretions for 3–4 days at titers of 101 –103 pfu/mL compared with titers in children that may be as much as 1000-fold higher and for more prolonged periods. Therefore, the low levels of virus shed by adults, as well as the thermolability of RSV, contribute to the insensitivity of viral culture and rapid antigen detection with enzyme immunoassays (EIAs) in this age group. Serological methods based on EIA using a purified virus or viral proteins such as the G and F glycoprotein appear to be more reliable in older adults, which may be due in part to the as yet unexplained observation of a more a vigorous IgG antibody response in adults older than 65 years than in younger adults. Although IgG serology has been shown to be very sensitive (90–95%), it is only useful in research settings since a ≥4-fold rise in titer (acute to convalescent) is needed for diagnosis. At the present time, there are currently no reliable IgM EIA assays in clinical use. However, the time required for a serological response assay and comparison between paired and convalescent-phase serum samples has not been useful for guidance of patient care.[3,5]

In contrast to the insensitivity of culture and antigen assays and the poor clinical utility of serological tests, molecular assays (nuclear acid amplification tests; NAATs) have become the gold standard in respiratory virus detection offering both high sensitivity and specificity. Widespread availability of uniplex RSV PCR assays, combined influenza and RSV PCR assays, and more recently a variety of multiplex RT-PCR assays that are able to detect as many as 15 common respiratory viruses now allow for rapid viral diagnosis with a turnaround time as short as 1 h for some assays. Disadvantages of RT-PCRs assays include the relatively high cost, which may prohibit use in smaller community hospitals, and the variation in cut-off thresholds for the different assays, which to date have not been standardized.[3]

Another approach to detect RSV is Direct fluorescent antibody (DFA) testing, that requires a swab that allows for an appropriate number of epithelial cells to be collected and is largely applicable to appropriately collected nasopharyngeal specimens. Specimens that lack enough cells or originate from other sites in the respiratory tract are not appropriate for this type of testing. However, depending on workflow and resources within the laboratory, DFA testing as an adjunct to molecular test methods may provide an

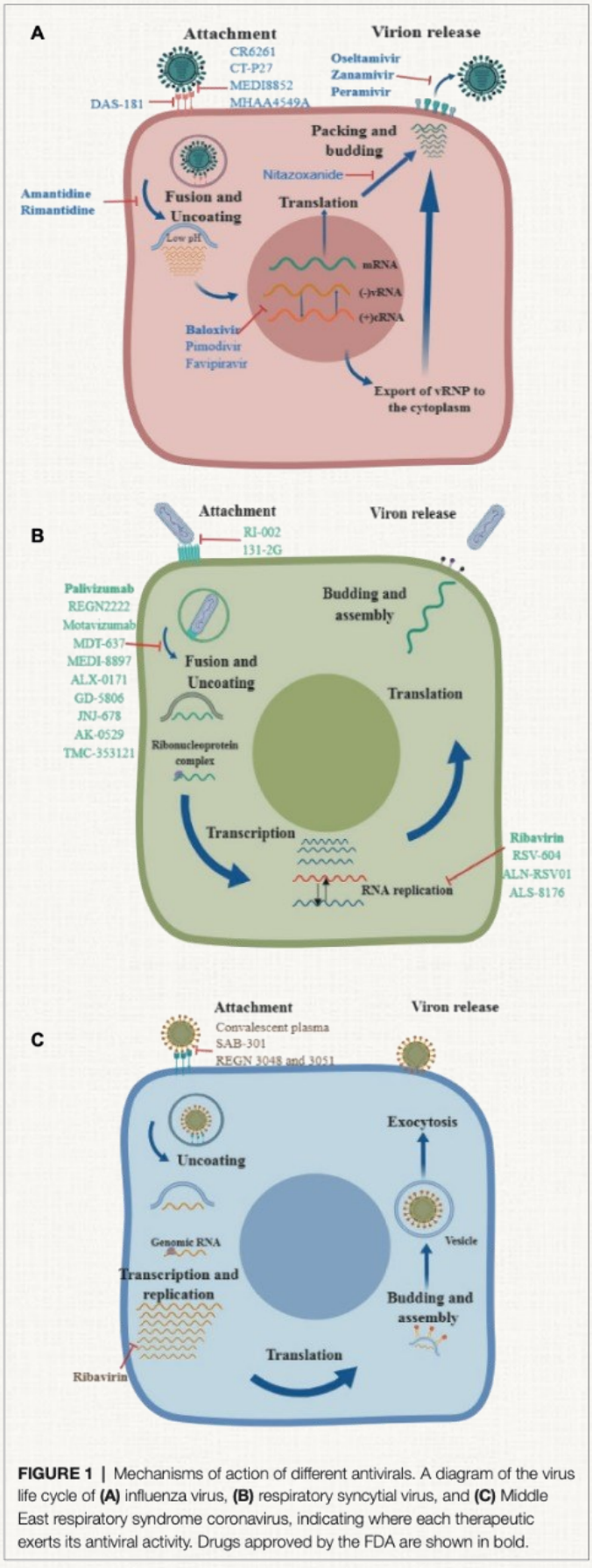
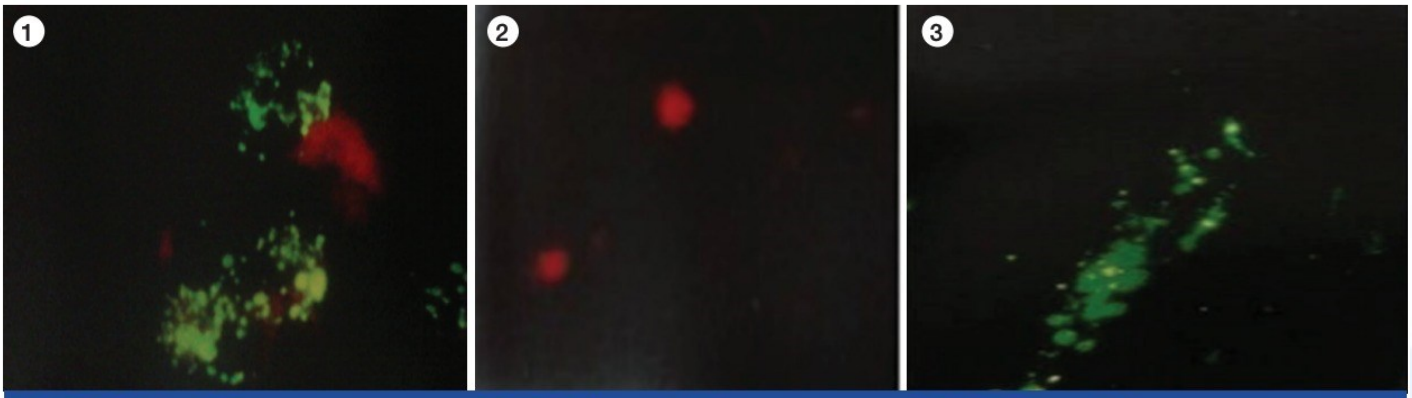


FIGURE 1 | Mechanisms of action of different antivirals. A diagram of the virus life cycle of **(A)** influenza virus, **(B)** respiratory syncytial virus, and **(C)** Middle East respiratory syndrome coronavirus, indicating where each therapeutic exerts its antiviral activity. Drugs approved by the FDA are shown in bold.



[Table/Fig-1]: Positive for RSV. [Table/Fig-2]: Negative for RSV. [Table/Fig-3]: Nonspecific fluorescence.

option for RSV testing in high-risk patients such as hematopoietic stem cell transplant patients. Prior to the broader utilization of easier-to-use molecular diagnostic assays, DFA testing historically provided a more rapid response than lab-developed and batched molecular assays for RSV. Other groups have identified that in pediatric populations, compared to nucleic acid amplification testing, DFA test sensitivities are probably highest in the first 3 days of infection.[5]

Treatment and Prevention

The high frequency of recurrent infections is indicative of the puzzling immune response to RSV and the difficulty of developing an effective vaccine. Naturally acquired immunity is neither complete nor durable. Nevertheless, protection against severe disease develops after primary infection. The components of the response providing this partial immunity are incompletely defined. Much of the current knowledge derives from the unfortunate first vaccine trials in the 1960s, which used a formalin-inactivated vaccine. Immunized children had more severe disease than controls when they were subsequently naturally infected with RSV; 80 percent required hospitalization, as compared with 5 percent of controls. RSV was isolated from the lower respiratory tract of two children who died, and their lungs contained eosinophilic infiltrates. Several abnormalities of the immune response to inactivated vaccine, as compared with the response to natural infection, were subsequently detected, which suggested that protection against RSV requires a balance between humoral and cellular immunity. Vaccinated persons lacked specific mucosal antibodies, and their serum antibodies had deficient neutralizing and fusion-inhibiting activity, suggesting that formalin inactivation selectively modified epitopes within the important surface glycoproteins G and F. In addition, peripheral eosinophilia and enhanced lymphocytic proliferative responses to RSV developed in some vaccinated persons.[6,7]

The reason for the enhanced respiratory disease was due, in part, to formalin-mediated destruction of neutralizing epitopes in the vaccine preparation. However, the antibodies that were induced by the formalin-inactivated vaccine were also poor in antibody affinity and avidity for viruses epitope and ultimately pathogenic due to poor TLR activation of B cells. That study underlines the need for RSV vaccines to be developed around rational subunit approaches that induce neutralizing antibodies to RSV in the airway mucosae. Due to less antigenic variability of the F protein compared with the G protein, this protein is the main target of research for developing antivirals as well as anti-RSV vaccines. Some promising examples of strategies currently under development are stabilized prefusion RSV-F proteins and other subunit vaccines that preserve key neutralizing epitopes on the RSV-F glycoprotein.[5]

There are currently several recombinant RSV subunit vaccines in clinical trials. In February 2016, Novavax (226) developed a vaccine that completed a phase II clinical trial. The efficacy of the Novavax vaccine was reported as a function of circulating neutralizing antibodies. RSV infection alone, without vaccine stimulation, will trigger the production of robust neutralizing antibodies in the circulation and strong cytotoxic T lymphocyte (CTL) memory. However, it has not been reported whether the Novavax vaccine elicits mucosal neutralizing IgA antibodies that better correlate with protection. A thorough investigation of the IgA response is important since RSV infection evades IgA B cell memory through unknown mechanisms and RSV is thus able to reinfect the host throughout his or her lifetime. So far, there is no indication that any of the vaccines currently in clinical trials elicit mucosal anti-RSV IgA neutralizing antibodies or long-term IgA B cell memory, two requirements for an RSV vaccine to confer a significant level of protection. In summary, it is too soon to tell whether the RSV vaccines that are in clinical trials will confer protection against RSV infection.[5]

If an RSV vaccine is eventually licensed, there is a strong likelihood that there will remain a need for RSV anti-infective medications. There are currently only two antivirals for RSV available, palivizumab for prevention and ribavirin for treatment. The biologic palivizumab (MedImmune, USA) is the only FDA-licensed drug that specifically targets RSV infection, and it has a benefit over RSV hyperimmune IVIG in that it can be delivered intramuscularly rather than intravenously. Palivizumab is a humanized monoclonal antibody that is directed against the RSV-F fusion protein expressed on the surface of the RSV virion. Palivizumab and the closely related motavizumab bind to an epitope within amino acid positions 258 and 275 in the RSV-F protein. Palivizumab is recommended by the American Academy of Pediatrics (AAP) to be administered to high-risk infants and young children likely to benefit from immunoprophylaxis based on gestational age and certain underlying medical conditions. It is given in monthly intramuscular injections during the RSV season, which generally occurs during

fall, winter, and spring in most locations in the United States. Although effective, palivizumab has limitations such as a reduced window of opportunity, the potential to produce drug-resistant viruses, and high cost. Currently, there is no efficacious treatment for active RSV infection.[8]

Currently, the only licensed drug for treating existing RSV infection is aerosolized ribavirin treatment of patients at the highest risk from RSV infection. The guanosine analog ribavirin is a broad-spectrum antiviral agent with activity against RSV and other RNA viruses such as hepatitis C and Zika viruses. The beneficial effect of this drug in inhibiting RSV replication was demonstrated in several studies. Numerous blinded trials of RSV-infected patients have demonstrated faster RSV clearance, decreased viral shedding, and shorter hospitalization stays with the use of ribavirin to treat RSV infection. Ribavirin showed antiviral activity against RSV and reduced RSV lung titers in infected cotton rats.[9] Similarly, significant clinical benefits have been observed in children treated with aerosolized ribavirin early in infection. In in-vitro study, RNA-seq analysis was used to investigate HRSV RNA synthesis in infected cells and cells treated with ribavirin. The data indicated that both transition and transversion mutations occurred in clusters along the hRSV genome. The frequency of transitions was increased in hRSV-infected cells treated with ribavirin and correlated with reductions in the abundance of viral RNA and in progeny virus, consistent with a loss of viral fitness. In brief, ribavirin treatment did indeed cause an increase in the number of mutations, which was associated with a decrease in virus production.[10] However, the clinical application of ribavirin is limited because of its nonspecific anti-RSV activity, risks for potential toxicity, and relatively high cost. The teratogenic effects of ribavirin in laboratory models and its cardiovascular contraindications at therapeutic doses mean that a cumbersome scavenging ventilation system is required for every ribavirin aerosol tent that is used to treat an RSV-infected patient. Safer drugs at lower therapeutic doses are needed to ensure that the next anti-RSV drugs see widespread use to prevent and treat RSV infection.[11]

New therapeutic options are required for the treatment of active RSV infection. RSV is a viable target for the development of antivirals, compared to viruses such as influenza virus, for example. Tamiflu is a neuraminidase inhibitor that has been marketed for the treatment of influenza, but the efficacy of Tamiflu has been questioned. This is due, primarily, to a brief therapeutic window of opportunity whereby Tamiflu must be administered prior to the peak of influenza viral load, which is within 48 h of influenza virus infection. Such a short window makes influenza difficult to treat because the onset of symptoms follows initial replication, leaving a mere few hours between transmission and therapeutic efficacy. With respect to the therapeutic window, RSV is an easier target than the influenza virus because the peak of RSV viral load is much later, up to 8 days post-infection. This leaves a number of days in the RSV therapeutic window to treat RSV, meaning, theoretically, that RSV should be an easier infection to treat than influenza.[12] Great advances have been made in the last few years, and several antivirals are currently under development, and many have reached early stages in clinical trials. This is a very exciting and evolving field that will continue producing more effective antivirals that are highly needed for the treatment of RSV.

In summary, RSV has long been acknowledged as the primary respiratory pathogens among young children. More recent is the recognition that this virus causes a considerable disease burden throughout life, such as asthma. The consequences of repeated infections are most marked in elderly and immunocompromised persons. Even in otherwise healthy persons, reinfections often require medical attention, but they are generally undiagnosed and unrecognized. However, these reinfections may spread from healthy persons to those at high risk. Future studies should focus on the analysis of RSV molecular epidemiology, evolution, and transmission with the aim of defining the circulating viruses and characterizing the antigenic variation. These studies might provide important implications for vaccine development and for finding new strategies to control the burden of RSV disease and identifying other viral proteins that could be targets of neutralizing antibodies. It is also interesting that there is still a lack of RSV study conducted in Indonesia, which indicates more research is needed to characterize the circulating RSV in Indonesia regions better.

Reference:

1. Collins, P. L. & Graham, B. S. Viral and Host Factors in Human Respiratory Syncytial Virus Pathogenesis. Journal of Virology 82, 2040–2055 (2008).
2. Sommer, C. Risk Factors for Severe Respiratory Syncytial Virus Lower Respiratory Tract Infection. The Open Microbiology Journal 5, 144–154 (2012).
3. Branche, A. R. & Falsey, A. R. Respiratory Syncytial Virus Infection in Older Adults: An Under-Recognized Problem. Drugs & Aging 32, 261–269 (2015).
4. Stadther, J. & Dennehy, P. H. Diagnosis of respiratory syncytial virus infection. Pediatric Infectious Disease Journal 7, 744–745 (1988).
5. Griffiths, C., Drews, S. J. & Marchant, D. J. Respiratory syncytial virus: Infection, detection, and new options for prevention and treatment. Clinical Microbiology Reviews 30, 277–319 (2017).
6. Hall, C. B. Respiratory Syncitial Virus and Parainflueza Virus1. Hall CB. Respiratory Syncitial Virus and Parainflueza Virus. English J. 2011;344(25):1917-1928. New England Journal of Medicine 344, 1917–1928 (2001).
7. KIM, H. W. H. A. et al. RESPIRATORY SYNCYTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE12. American Journal of Epidemiology 89, 422–434 (1969).
8. SIVA SUBRAMANIAN, K. N. et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. The Pediatric Infectious Disease Journal 17, (1998).
9. Bonavia, A. et al. identification of broad-spectrum antiviral compounds and assessment of the druggability of their target for efficacy against respiratory syncytial virus (RSV). Proceedings of the National Academy of Sciences of the United States of America 108, 6739–6744 (2011).
10. Aljabr, W. et al. Investigating the Influence of Ribavirin on Human Respiratory Syncytial Virus RNA Synthesis by Using a High-Resolution Transcriptome Sequencing Approach. Journal of Virology 90, 4876–4888 (2016).
11. Behzadi, M. A. & Leyva-Grado, V. H. Overview of Current Therapeutics and Novel Candidates Against Influenza, Respiratory Syncytial Virus, and Middle East Respiratory Syndrome Coronavirus Infections . Frontiers in Microbiology 10, 1327 (2019).
12. Bagga, B. et al. Comparing inluenza and RSV viral and disease dynamics in experimentally infected adults predicts clinical effectiveness of RSV antivirals. Antiviral Therapy 18, 785–791 (2013).

INA-RESPOND Newsletter

STIGMA AND INFODEMIC: WHY DO WE CREATE OUR ENEMIES?

By: Aly Diana

COMIC CORNER

"Let hope be the antidote to fear. Let solidarity be the antidote to blame. Let our shared humanity be the antidote to our shared threat."

-WHO Director-General: Tedros Adhanom Ghebreyesus-

Since the emergence of COVID-19 we have seen many news of public stigmatization among specific populations, and the rise of harmful stereotypes. Social stigma in the context of health is the negative association between a person or group of people who share certain characteristics and a specific disease. In an outbreak, this may mean people are labelled, stereotyped, discriminated against, treated separately, and/or experience loss of status because of a perceived link with a disease. Such treatment can negatively affect those with the disease, as well as their caregivers, family, friends and communities. People who don't have the disease but share other characteristics with this group may also suffer from stigma.

The current COVID-19 outbreak has provoked social stigma and discriminatory behaviours against people of certain ethnic backgrounds as well as anyone perceived to have been in contact with the virus. There are also an increasing number of reports of public stigmatization against people from areas affected by the epidemic. Stigma can also occur after a person has been released from COVID-19 quarantine even though they are not considered a risk for spreading the virus to others.

The level of stigma associated with COVID-19 is based on three main factors: 1) it is a disease that's new and for which there are still many unknowns; 2) we are often afraid of the unknown; and 3) it is easy to associate that fear with 'others'. It is understandable that there is confusion, anxiety, and fear among the public. Unfortunately, these factors are also fuelling harmful stereotypes.

Stigma can: 1) Drive people to hide the illness to avoid discrimination; 2) Prevent people from seeking health care immediately; 3) Discourage them from adopting healthy behaviours. Such barriers could potentially contribute to more severe health problems, ongoing transmission, and difficulties controlling infectious diseases during an infectious disease outbreak.

We can do our part in preventing and stopping stigma. We all need to be intentional and thoughtful when communicating on social media and other communication platforms, showing supportive behaviors around COVID-19.

First thing first, let us spread the facts; as stigma can be heightened by insufficient knowledge about how the new coronavirus disease (COVID-19) is transmitted and treated, and how to prevent infection. Let us stop the infodemics; as stigma can be worsen by excessive amount of information about a problem that makes it difficult to identify a solution. Infodemics can spread mis- and dis-information and rumors during a health emergency. Infodemics can hamper an effective response and create confusion and distrust among people.

We know that every outbreak will be accompanied by a kind of tsunami of information, and within this information we always have misinformation, rumours, etc. We know that this phenomenon has existed since a long time ago. However, with the contribution of social media in this era, this phenomenon is amplified, it goes faster and further, like the viruses that travel with people and go faster and further. The real thing at stake during an outbreak is making sure people will do the right thing to control the disease or to mitigate its impact. It is not only spreading information to make sure people are informed; but also making sure people are informed to act appropriately.

Note: This article has been written mainly using the words from the main sources. The main purpose is to spread the messages from World Health Organization and Centres for Disease Control and Prevention regarding stigma and infodemic.

Please visit WHO Information Network for Epidemics website (https://www.epi-win.com/advice-and-information) for more actual information.

References:

WHO Director-General's opening remarks at the media briefing on COVID-19 - 9 March 2020; https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---9-march-2020

WHO, Coronavirus disease 2019 (COVID-19) Situation Report – 35;

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200224-sitrep-35-covid-19.pdf?sfvrsn=1ac4218d_2

CDC, COVID-2019, Stigma and Resilience; https://www.cdc.gov/coronavirus/2019-ncov/about/related-stigma.html

Zarocostas J. How to fight an infodemic. The Lancet: World Report; 395 (10225), p676; https://doi.org/10.1016/S0140-6736(20)30461-X

IFRC, Unicef, WHO, Social stigma associated with COVID-19: A guide to preventing and addressing social stigma; https://www.epi-win.com/sites/epiwin/files/content/attachments/2020-02-24/COVID19%20Stigma%20Guide%2024022020_1.pdf

World Health Organization

Coping with stress during the 2019-nCoV outbreak

It is normal to feel sad, stressed, confused, scared or angry during a crisis.

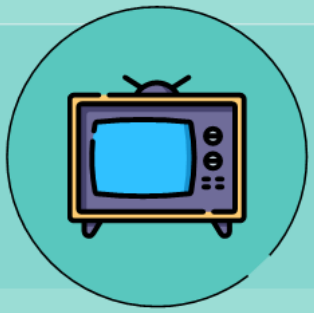
Talking to people you trust can help. Contact your friends and family.

If you must stay at home, maintain a healthy lifestyle - including proper diet, sleep, exercise and social contacts with loved ones at home and by email and phone with other family and friends.

Don't use smoking, alcohol or other drugs to deal with your emotions.

If you feel overwhelmed, talk to a health worker or counsellor. Have a plan, where to go to and how to seek help for physical and mental health needs if required.

Get the facts. Gather information that will help you accurately determine your risk so that you can take reasonable precautions. Find a credible source you can trust such as WHO website or, a local or state public health agency.



Limit worry and agitation by lessening the time you and your family spend watching or listening to media coverage that you perceive as upsetting.

Draw on skills you have used in the past that have helped you to manage previous life's adversities and use those skills to help you manage your emotions during the challenging time of this outbreak.

INA-RESPOND Newsletter

EXERCISE AND LOW BACK PAIN

By: Caleb Leonardo Halim

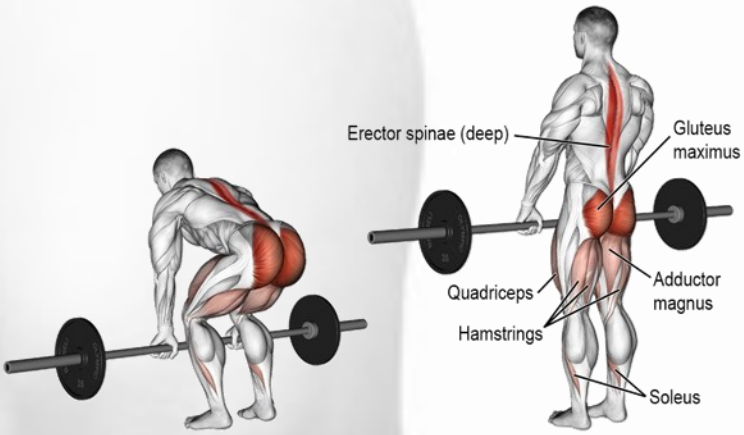
Low back pain is a condition that most people have experienced at least once in their lifetime. It is a prevalent health problem in the world and a major cause of disability, affecting performance at work and general well being. Low back pain affects people of all ages, from children to the elderly, and it is a common reason for medical consultations. Approximately 50 –80% of adults experience low back pain at some point in their life. The prevalence of low back pain ranges from 11%-84% in a low-income country and 30% in a high-income country.[1] The prevalence and incidence of low back pain increase with age. Though several risk factors have been identified (occupational posture, depressive moods, obesity, and body height), the causes of low back pain remain obscure, and its diagnosis is difficult to make. Back pain is not a disease but a constellation of symptoms.[2]

Low back pain is categorized into mechanical or non-mechanical. Mechanical low back pain arises intrinsically from the spine, intervertebral disks, or surrounding soft tissues such as muscles. Structural problems such as malalignment of the spine (known as scoliosis) and tightness of the muscles surrounding the lower back are the cause of most low back pain. For scoliosis, doctors need to conduct plain radiography of the spine to confirm the diagnosis. Muscle tightness in the lower back, which is the other cause of most lower back pain, is usually caused by acute or repetitive exposure of some incorrect movement or some heavy loads. On the other hand, clinical signs and symptoms, or red flags, may help identify cases of non-mechanical low back pain. These red flags include progressive motor or sensory loss, new urinary retention or overflow incontinence, history of cancer, recent invasive spinal procedure, and significant trauma relative to age.

Low back pain has affected many people. Many office workers suffered from low back pain because of their behind-the-desk sitting form while working. Drivers do not feel so good on their back after driving a vehicle for a long time. A lot of parents feel tightness and pain on their back after carrying their baby for an extended period. Some people may experience low back pain after picking something from the floor. Incorrect posture while doing activities may provoke low back pain. Therefore, it is essential to know the proper posture while doing certain actions to prevent low back pain.[3]

Low back pain can be prevented not just by doing the correct position/posture but also by strengthening our body. Many studies have reported the benefits of strength training on the health and fitness of our bodies. Strength training can enhance our core, so the body becomes more stable while making

movements or while maintaining body position for a long time in a certain position. So, why is strength training essential for the spine? Repair of injury to soft tissue is an issue of cellular nutrition. The better the supply of nutrients to the injured area, the better the opportunity for that tissue to become healthy. Strengthening the extensors of the low back encourages blood flow to the area of injury, and consequently, enhances the opportunity for healing to take place. Blood flow may be occluded during exercise, but immediately following the exercise, fresh blood and nutrients flood the trained muscle. From a clinical standpoint, aggressive strength training of the lumbar spine has been shown to overcome structural weaknesses in patients with low back pain. It will prevent malalignment from the spine and tightness from the lower back muscles that occur due to weakness, which in the end will prevent low back pain.[4,5]

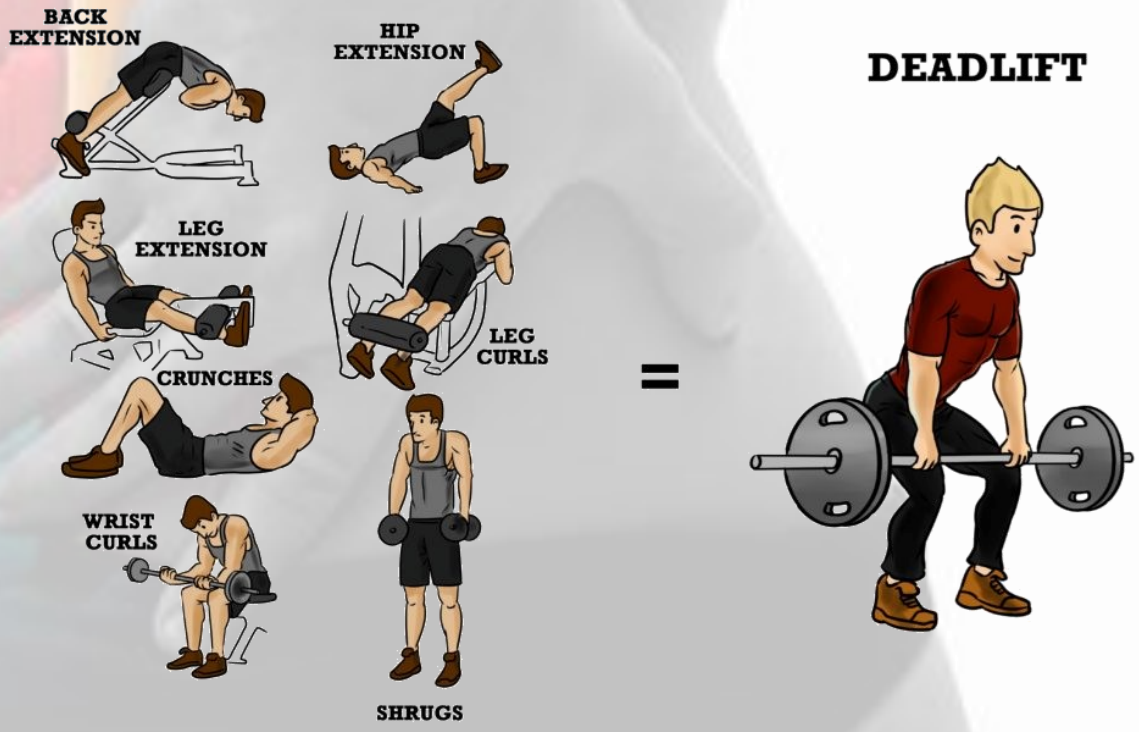


All exercises are safe to do, but we do need to choose some exercise over others if we are suffering from low back pain. Choose exercise movement that does not worsen your pain, and for those who are not currently suffering from back pain, you can choose any strength training you like, of course, while still paying attention to the form of the movement. Strength training recommendation for low back pain is still the same as that of any other strength training; 2-3 times a week focusing on getting stronger on lower back muscles, abs, and side abs. These muscles will help to maintain the body in a stable position. The deadlift is the most controversial strength training movement. While many people think this training will cause low back pain and harm for our spine, studies showed otherwise. Deadlift could strengthen our muscles. While doing a deadlift, almost all muscles in our body contract to create the movement. Most importantly, it heavily trains our core muscles. Finally, and most importantly, we need to keep our bodies moving. Do not just stay in one position, especially in a sitting position for a long time; Try to do some strength training instead.

In the end, we all want to live pain-free and have a good quality of life, right? So, start to train your body today.[6,7]

References:

1. Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010;24:769–781.
2. Francis F. Tadesse G, Isaac O. Real-world incidence and prevalence of low back pain using routinely collected data. Rheumatology International. 2019;39:619–626.
3. Will JS, Bury DC, Miller JA. Mechanical Low Back Pain. Am Fam Physician. 2018;98:421-428.
4. Hart PD, Buck DJ. The effect of resistance training on health-related quality of life in older adults: Systematic review and meta-analysis. Health Promot Perspect. 2019;9:1–12.
5. Dreisinger TE. Strength training and low back pain. National Strength and Conditioning Association. 2003;25:56-9.
6. Berglund L, Aasa B, Hellqvist J, Michaelson P, Aasa U. Which Patients With Low Back Pain Benefit From Deadlift Training?. J Strength Cond Res. 2015;29:1803-11.
7. Berglund L. Deadlift training for patients with mechanical low back pain: A comparison of the effects of a high-load lifting exercise and individualized low-load motor control exercises. 2016



INA-RESPOND website: www.ina-respond.net

INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

The INA-RESPOND newsletter welcomes all network members and stakeholders to contribute by submitting articles related to the network's studies and interests. Send your articles or subscribe to our latest newsletter by sending an email to INA.Secretariat@ina-respond.net